REMARKS

Claims 1-48, 53, 66, and 67 are canceled. Claim 70 is amended. Claims 49-52, 54-65, 68, and new claims 69-70 are pending and are rejected.

Priority Claim

The Examiner has acknowledged that Applicant is entitled to an October 28, 2003 priority date.

Claim Objection

The Examiner's objection to claim 70 is overcome by the present amendment.

Rejections under 35 U.S.C. § 103(a)

The Office rejects claims 49-52, 54-65, and 68, which are directed to methods for inducing new blood vessel growth in myocardial tissue and improving cardiac function, under 35 U.S.C. § 103(a) as obvious over International Publication No. Isner et al., WO 97/14307, (hereinafter "Isner"), in view of Hammond et al., U.S. Patent No. 5,880,090, (hereinafter "Hammond"), and U.S. Patent No. Dillman et al., 6,605,274 (hereinafter "Dillman"). For the reasons detailed below, Applicants respectfully disagree with the rejection and request that it be withdrawn.

The test of obviousness requires that one compare the claim's "subject matter as a whole" with the prior art "to which said subject matter pertains." 35 U.S.C. §103(a). The inquiry is fact-specific and must include i) the scope and content of the prior art; ii) the differences present between the prior art and the claimed invention; iii) the level of ordinary skill in the art at the time of filing; and iv) objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 149 USPQ 159, 467, 86 S. Ct. 684 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. *In re Fine*, 837 F.2d 1071,1075, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). To prevent the use of hindsight based on

the invention to defeat patentability, the Federal Circuit requires the Examiner to show a motivation to combine the references that create the case of obviousness. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). The Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *Id.* When the references cited by the Patent Office fail to establish a *prima facie* case of obviousness, the rejection is improper and must be withdrawn. *In* re Fine, 837 F.2d at 1074, 5 U.S.P.Q.2d at 1598.

Isner

The Examiner has considered the scope and content of Isner and acknowledged that differences exist between the prior art and the claimed invention. In particular, the Examiner asserts that Applicants' claimed invention differs from that of Isner because Isner fails to teach the administration of an effective amount of stem cell factor, colony stimulating factor to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells as presently claimed. With respect to endothelial progenitor cells, the Examiner states:

> Isner does not teach specifically a further administration of an effective amount of at least one angiogenic factor, specifically a stem cell factor (SCF), a colony stimulating factor (CSF), or an effective fragment thereof into the mammal to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells. (Office action mailed March 25, 2008, page 6, first paragraph; emphasis present in the original.)

Relevant to this point, Applicants specification describes methods for modulating EPC kinetics by administering cytokines (Example 1, page 29). In particular, Applicants describe the use of cytokines to increase the number of circulating endothelial progenitor cells (page 29, lines 11-26). In addition, Applicants teach that such endothelial progenitor cells increase neovascularization of ischemic tissues (pages 29-30). Applicants report that their results indicate that "GM-CSF exerts a potent stimulatory effect on EPC kinetics and that such cytokine-induced EPC mobilization can enhance neovascularization of severely ischemic tissues as well as de novo vascularization of previously avascular sites (page 36, lines 24-28). These results, which the Examiner states were not described by Isner, represent a significant advance over the prior art.

In addition, the Examiner indicates that Isner fails to teach methods for monitoring cardiac function. The Examiner states: "Isner also does not teach specifically to monitor a cardiac function by one of the recited approaches." (Office action mailed March 25, 2008, p. 6, first paragraph; emphasis present in the original.) Relevant to this point, Applicants' specification describes the use of VEGF-2 in a mouse model of myocardial ischemia, and the use of G-CSF and VEGF-2 in a swine model of myocardial ischemia. Surprisingly, Applicants discovered that this treatment resulted in a marked increase in cardiac function (Example 11, pages 47-48), which was associated with the recruitment of bone marrow cells to ischemic cardiac tissues (page 57, lines 16-21). Applicants' results showing that the claimed methods induce new blood vessel growth in myocardial tissue and improve cardiac function provided a significant advance over the prior art. Applicants claimed invention is based, at least in part, on this important discovery.

Applicants' claims recite monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension (LVEDD), end-systolic dimension (LVESD), fractional shortening (FS), wall motion score index (WMSI), electromechanical mapping, cardiac angiography or LV systolic pressure (LVSP). The Examiner indicates that this feature distinguishes Applicants' claimed invention from that of Isner (Office action mailed March 25, 2008, page 6, first paragraph). To remedy the alleged deficiency in Isner, the Examiner cites Dillman.

Dillmann

Dillmann describes methods for monitoring the function of a cardiac tissue. The Examiner asserts that it would be obvious for the skilled artisan to monitor the effects of the treatment described by Isner by monitoring cardiac function using the methods described by Dillmann. Applicants respectfully disagree. As discussed above, in order to establish a prima facie case of obviousness, the Federal Circuit requires the Examiner to show some motivation to combine the references that create the case of obviousness. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). A teaching, suggestion, or motivation to combine cannot be merely derived from the fact that the combination could be made, rather the motivation "must be clear and particular." *In re Dembiczak*, 175 F.3d 994, 50 USPQ 2d 1614

(Fed. Circ. 1999). The Federal Circuit cautions against inferring the presence of such motivation where it lacks this particularity. The Court states:

> Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

In sum, it is not sufficient to show that Applicants' claimed combination *could* be made. Rather, the Examiner must show some particular teaching or suggestion within the references themselves that the combination *should* be made.

Hammond

The Examiner cites Hammond as disclosing the use of stem cell factor and granulocyte macrophage colony stimulating factor for the mobilization of endothelial cell progenitors. Applicants note that the use of such factors is recited only in claims 58 and 68.

In contrast to Applicants claims, which are directed to methods for inducing new blood vessel growth in myocardial tissue and improving cardiac function Hammond, Hammond describes methods for coating a ***synthetic vascular graft*** with endothelial cells. Such methods are clearly different from the claimed invention which recites methods for inducing blood vessels in myocardial tissue. First, the grafts described by Hammond are entirely synthetic and comprise polyethylene terephthalate and polytetrafluoroethylene. The usefulness of such grafts is limited by their tendency to promote clot formation (column 1, lines 15-26). To overcome such limitations, Hammond describes methods for increasing the number of endothelial cells that ***attach to and coat the surface*** of synthetic grafts (column 1, line 60, to column 2, line 5). Not only are such synthetic grafts plainly distinct from a myocardial tissue, but the process for forming an endothelial coating on such a graft is clearly different from the process required to generate new blood vessel within a tissue. Hammond teaches that endothelialization promoting agents (e.g., GM-CSF, G-CSF) enhance "**adherence of circulating endothelial cells to graft surfaces**, or may stimulate the multiplication of blood-borne endothelial precursors that have become **adhered**." (column 2, lines 64-67.) Hammond teaches that this process relies on "'fallout endothelialization.' More specifically, it has been proposed that the circulating cells

give rise to endothelial coatings of vascular prostheses . . . " Methods for increasing the number of endothelial cells that adhere to and coat a synthetic graft are distinctly different from the multifaceted biological processes that regulate blood vessel formation within a myocardial tissue. Moreover, like the other references, Hammond fails to teach or suggest Applicants claimed invention which recites that the claimed method improves cardiac function. Furthermore, one skilled in the art would lack the requisite expectation of success to combine the methods of increasing synthetic graft endothelialization described by Hammond with any other method described in the references cited by the Office to arrive at Applicants' claimed combination. Thus, the Office has failed to establish a *prima facie* case of obviousness, and for this reason alone the rejection of the claims as obvious over Isner, in view of Hammond and Dillman should be withdrawn.

Asahara

The Examiner further rejects claims 50, 51, and 57 under 35 U.S.C. § 103(a) over Isner, Hammond, Dillman and Asahara et al., (EMBO J. 18:3964-3972, 1999; hereinafter "Asahara"). Asahara teaches that "VEGF-induced mobilization of bone marrow-derived EPCs resulted in increased differentiated EPCs *in vitro* and augmented corneal neovascularization *in vivo*." Asahara describes the use of VEGF to induce the mobilization of bone marrow-derived EPCs, and notes that these EPCs can contribute to corneal neovascularization. Asahara failed to teach or suggest that VEGF should be used to induce new blood vessel growth in a myocardial tissue to improve the function of that tissue. In addition, Asahara failed to appreciate, as Applicants' did, that the **combination** of a nucleic acid encoding at least one angiogenic protein and at least one angiogenic factor, enhances the induction of blood vessel growth in a myocardial tissue. Asahara plainly teaches that VEGF is sufficient to induce vasculogenesis. To the extent that Asahara directs the skilled artisan towards the use of VEGF to induce vasculogenesis, he teaches away from Applicants' claimed invention, which recites administering to a mammal an effective amount of VEGF **and** a nucleic acid encoding at least one angiogenic protein. Thus, Asahara also fails to teach or suggest Applicants' claimed invention, and the rejection of the claims over Isner, Hammond, Dillman and Asahara should also be withdrawn.

Coleman and Hu

The Examiner further rejects claim 70 over Isner, in view of Hammond, Dillman, and further in view of Coleman (U.S. 7,273,751; hereinafter "Coleman") or Hu (U.S. 6,734,285; hereinafter "Hu"). The Examiner acknowledges that Isner, Hammond and Dillman fail to describe the use of VEGF-2 to new blood vessel growth in myocardial tissue and improve cardiac function. To remedy the deficiencies of Isner, Hammond and Dillman the Examiner now cites Coleman and Hu. The Examiner indicates that Coleman and Hu describe the use of VEGF-2 as an angiogenic factor. Specifically, the Examiner states:

> Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the method of Isner, Hammond et al and Dillman et al. by also administering to the treated mammal an effective amount of a nucleic acid encoding VEGF-2 in to the myocardial tissue in light of the teachings of either Coleman or Hu.
>
> An ordinary skilled artisan would have been motivated to carry out the above modifications because both Coleman and Hu et al already taught separately that VEGF-2 is a potent angiogenic factor . . .

The Examiner relies on Hu and Coleman to provide the motivation to use VEGF-2 in combination with a nucleic acid encoding at least one angiogenic protein to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells. However, the Examiner's reliance on these references is misplaced. Hu and Coleman fail to provide the necessary motivation to use VEGF-2 in combination with a nucleic acid encoding an angiogenic protein. Hu and Coleman both teach that VEGF-2 is efficacious on its own, and neither of these references teaches that it is necessary or desirable to administer VEGF-2 in combination with another factor.

Applicants were the first to appreciate that blood vessel growth could be induced using such methods, and that the growth of such blood vessels would improve cardiac function. It is not sufficient that one **could** have made the combination, the cited references must suggest the desirability of making the claimed combination and must further indicate that **the combination if made would have succeeded**. None of the references cited by the Office, alone or in any combination, teaches or suggests Applicants' claimed invention.

Furthermore, Applicants note that the Examiner relies on no less than five references in making the obviousness rejection. Applicants submit that such reliance belies the alleged

obviousness of the claimed invention. *Hybritech, Inc. v. Monoclonal Antibodies*, Inc., 802 F.2d 1367, 1383 (Fed. Cir. 1986). "The large number of references, as a whole, relied upon by the district court to show obviousness, about twenty in number, skirt all around but do not as a whole suggest the claimed invention, which they must, to overcome the presumed validity." *Id.* at 1383. While the number of references is not determinative, "the requisite prior art suggestion to combine becomes less plausible when the necessary elements can only be found in a large number of references." 2 Chisum on Patents § 5.04[1][e][vi].

In sum, the Office has failed to establish a *prima facie* case of obviousness, and the rejection of the claims under U.S.C. § 103(a) should be withdrawn.

Double Patenting

Applicants acknowledge that claims 49-52, 54-65, and 68 are provisionally rejected over copending U.S. application No. 10/714,574. With regard to the provisional double patenting rejection over copending application No. 10/714,574, Applicants submit that upon consideration and entry of the instant Amendment and Response, the provisional double-patenting rejection will be the only rejection remaining in the instant application. Therefore, pursuant to M.P.E.P. § 822.01, Applicants respectfully request that the provisional obviousness-type double patent application be withdrawn so that the instant application may proceed to allowance.

CONCLUSION

In view of the above amendment and Remarks, Applicants believe the pending application is in condition for allowance.

Applicants believe that no fee is due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

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Respectfully submitted,

By _____

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